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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/082,544	02/20/2002	Frederick B. Oleson JR.	CUB-1 CON	8363

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EXAMINER
CHOI, FRANK I

ART UNIT	PAPER NUMBER
1616	4

DATE MAILED: 05/21/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/082,544	OLESON ET AL.	
	Examiner	Art Unit	
	Frank I Choi	1616	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 February 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-15 and 26* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-15 and 26* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *20 February 2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 2 .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Examiner notes that the rejections herein, except as provided for in the double patenting rejection below, are not intended to and does not apply to subject matter which was found to be allowable in US Pat. App. No. 09/406,568.

Priority

Preliminary amendment (2/20/2002) amended the Specification to claim priority to US Pat. App. No. 09/406,568, however, it incorrectly indicated that the filing date of said application was September 25, 1999. The correct date is September 24, 1999.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-15, 26 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over the claims of copending Application No. 09/406,568. Although the conflicting claims are not identical, they are not patentably distinct from each other because they claim similar subject matter, i.e. a method of

delivering daptomycin in dosage intervals, including intervals that do not result in muscle toxicity and in combination with other antibiotics.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-4, 11, 13-15, 26 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods of adminstering daptomycin such that it does not cause muscle toxicity, does not reasonably provide enablement for methods of administering daptomycin derivatives, A54145, A54145 derivatives or other lipopeptide antibiotics in such a manner that they do not cause muscle toxicity. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims. The only working examples provided are for daptomycin and combinations with other antibiotic drugs do not appear to have been tested as to compatibility or effect on muscle toxicity. It is well known in the art that even structurally similar antibiotics can have different modes and ranges of toxicity (Remington's, pp. 1176-1213. As such, without working examples a skilled artisan would be required to perform undue experimentation in order to determine first whether the same also cause muscle toxicity

and second the suitable doses and intervals which would not exhibit muscle toxicity for the dantomycin derivatives, A54145 or A54145 derivatives or other lippeptide antibiotics.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 6-15,26 are rejected under 35 U.S.C. 112, second paragraph, as failing to set forth the subject matter which applicant(s) regard as their invention. Evidence that the claims fail to correspond in scope with that which applicant(s) regard as the invention can be found in pg. 5 of the Specification. In the Specification, it appears that a essential element of the invention is that it does not cause muscle toxicity, however, Claims 6-10, 12-15 do not appear to have this limitation in the claims and claims 11 and 26 do not require that the claims contain said limitations.

Claim Rejections - 35 USC § 102/103

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-5, 26 are rejected under 35 U.S.C. 102(b) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Pryka et al. (DICP The Annals of Pharmacotherapy 24:255-56 (1990)).

Pryka et al. expressly disclose a method of administering daptomycin at a dose of 2mg/kg every 24 hours falling within the scope of applicant's claims (See entire document, especially the abstract).

Alternatively, at the very least the claimed invention is rendered obvious within the meaning of 35 USC 103, because the prior art discloses products and uses that contain the same exact ingredients/components as that of the claimed invention. See o In re May, 197 USPQ 601, 607 (CCPA 1978). See also Ex parte Novitski, 26 USPQ2d 1389, 1390-91 (Bd Pat. App. & Inter. 1993).

Claims 1-10, 26 are rejected under 35 U.S.C. 102(b) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Kennedy et al. (Antimicrobial Agents and Chemotherapy 33: 1522-25 (1989)).

Kennedy et al. expressly disclose a method of administering daptomycin at a dose of 10mg/kg as a single daily dose falling within the scope of applicant's claims (See entire document, especially the abstract).

Alternatively, at the very least the claimed invention is rendered obvious within the meaning of 35 USC 103, because the prior art discloses products and uses that contain the same exact ingredients/components as that of the claimed invention. See o In re May, 197 USPQ 601,

607 (CCPA 1978). See also Ex parte Novitski, 26 USPQ2d 1389, 1390-91 (Bd Pat. App. & Inter. 1993).

Claims 1-5, 11-15, 26 are rejected under 35 U.S.C. 102(b) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Van der Auwera (Antimicrobial Agents and Chemotherapy 33:1783-1790 (1989)).

Van der Auwera expressly discloses a method of administering daptomycin in a single dose of 1 or 2 mg/kg combined with amikacin falling within the scope of applicant's claims (See entire document, especially the abstract).

Alternatively, at the very least the claimed invention is rendered obvious within the meaning of 35 USC 103, because the prior art discloses products and uses that contain the same exact ingredients/components as that of the claimed invention. See o In re May, 197 USPQ 601, 607 (CCPA 1978). See also Ex parte Novitski, 26 USPQ2d 1389, 1390-91 (Bd Pat. App. & Inter. 1993).

Claims 1-33 rejected under 35 U.S.C. 103(a) as being unpatentable over the acknowledged prior art in view of Pryka et al., Kennedy et al. and Van der Auwera (same documents as above).

Applicant acknowledges that it is known in the art that low doses of daptomycin do not cause muscle toxicity, but that higher doses may be necessary to treat resistant strains (Specification pg. 3, lines 22-26). It is known in the art that 4 mg/kg doses at intervals of 12 hours is toxic to muscles but that single doses (0.5-6 mg/kg) or every 24 hour doses (1 or 2 mg/kg) of daptomycin were well tolerated (pg. 2, lines 24-29, pg. 3, lines 1-13. It is known in

the art that quinupristin/dalfopristin at 7.5 mg/kg at intervals of 8 or 12 hours caused muscle pain (pg. 3-14).

Pryka et al., Kennedy et al. and Van der Auwera teach that higher doses of daptomycin given in a single dose or at least every 24 hours are effective in treating infections and are well tolerated. Further, Van der Auwera teaches that daptomycin may be combined with other antibiotics.

The difference between the prior art and the claimed invention is that the prior art does not expressly disclose that certain higher doses of daptomycin administered at 24 hour intervals or longer will not be toxic to muscles. However, the prior art suggests that higher doses are well tolerated at intervals of 24 hours. As such it would have been well within the skill of and one of ordinary skill in the art would have been motivated to modify the prior art as above with the expectation that increasing the interval between doses would allow higher doses of the above mentioned antibiotics while keeping muscle toxicity to a minimum. Further, it would have been well within the skill of one skilled in the art to arrive at the various doses and intervals by optimization of the prior art values taking into consideration adverse effects on the patient and effective therapeutic range.

Therefore, the claimed invention, as a whole, would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, because every element of the invention has been collectively taught by the combined teachings of the references.

Claims 1-15, 26 are rejected under 35 U.S.C. 103(a) as being unpatentable over the acknowledged prior art in view Baker et al. (US Pat. 5,912,226), Woodworth et al.

(Antimicrobial Agents and Chemotherapy 36:318-325, 1992), Watanakunakorn (Antimicrobial Chemotherapy 19:445-48 (1987)), Thibault et al. (Life Sciences 22:1877-87 (1995) and Leclercq et al. (Antimicrobial Agents and Chemotherapy 35:92-98 (1991)).

Applicant acknowledges that it is known in the art that low doses of daptomycin do not cause muscle toxicity, but that higher doses may be necessary to treat resistant strains (Specification pg. 3, lines 22-26). It is known in the art that 4 mg/kg doses at intervals of 12 hours is toxic to muscles but that single doses (0.5-6 mg/kg) or every 24 hour doses (1 or 2 mg/kg) of daptomycin were well tolerated (Specification, pg. 2, lines 24-29, pg. 3, lines 1-13).

Baker et al. (U.S. Pat. 5,912,226) teach that LY146032 can be used orally, intramuscularly or intravenously and that the effective dose is about 0.1 to 100 mg/kg of the compound and can be administered as a single daily dose for extended periods of time and that the amount/dose or total amount is dependent on the nature and severity of the infection, age and health of the patient, tolerance of the patient to the antibiotic and microorganism(s) involved (Column 9, lines 50-68. Column 10, Column 11, lines 1-10).

Woodworth et al. teach that the administration of successive single doses of 2, 3, 4, and 6 mg/kg were well tolerated and that no adverse events were reported or observed and the doses were effective ex vivo against bacteria (Pgs. 321, 323, 324).

Watanakunakorn teaches that LY 146032 acts synergistically with gentamicin or tobramycin (see entire document, especially the abstract).

Thibault et al. teach that daptomycin protects against gentamicin nephrotoxicity (see entire document especially the abstract).

Leclercq et al. teach that combinations of antibiotics act synergistically (see entire document, especially the abstract).

The difference between the prior art and the claimed invention is that the prior art does not expressly disclose a method of administering at doses intervals that do not result in muscle toxicity in combination with other antibiotics. However, the prior art amply suggests the same as it is known in the art that daptomycin in single daily doses are well tolerated and resulted in no adverse reactions, that combinations of antibiotics synergistically, and that daptomycin has been shown to prevent gentamicin induced nephrotoxicity. As such, it would have been well within the skill of and one of ordinary skill in the art would have been motivated to administer doses at intervals of 24 hours or higher with the expectation that said administration would not cause muscle toxicity and be effective in treating various diseases.

Therefore, the claimed invention, as a whole, would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, because every element of the invention has been collectively taught by the combined teachings of the references.

Conclusion

A facsimile center has been established in Technology Center 1600. The hours of operation are Monday through Friday, 8:45 AM to 4:45 PM. The telecopier numbers for accessing the facsimile machines are (703) 308-4556 or (703) 305-3592.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Frank Choi whose telephone number is (703) 308-0067. Examiner maintains a flexible schedule. However, Examiner may generally be reached Monday-Friday, 8:00 am – 5:30 pm (EST), except the first Friday of the each biweek which is Examiner's normally scheduled day off.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's Supervisor, Mr. José Dees, can be reached on (703) 308-4628. Additionally, Technology Center 1600's Receptionist and Customer Service can be reached at (703) 308-1235 and (703) 308-0198, respectively.

FIC
May 18, 2002

JOHN PAK
PRIMARY EXAMINER
GROUP 1600